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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/757,100	01/09/2001	Brett P. Monia	ISPH-0533	6913

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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/757,100	Monia et al.
Examiner	**Art Unit**
Karen A. Lacourci re	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 45-58 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 45-58 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Applicant should note, the Office has corrected the submitted CRF of the sequence listing by deleting non-ASCII "garbage" at the end of files and has corrected the amino acid numbers for SEQ ID NO:2. No action is required on the part of the Applicant in regards to the sequence listing.

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-33, drawn to an antisense compound targeted to a nucleic acid encoding Fas, classified in class 536, subclass 24.5.

   II. Claims 34-38, drawn to a method of treatment using an antisense compound targeted to a nucleic acid encoding Fas, classified in class 514, subclass 44.

   III. Claim 39, drawn to a method of preventing cell migration using an antisense compound targeted to a nucleic acid encoding Fas, classified in class 514, subclass 44.

   IV. Claim 40, drawn to a method of preventing neovascularization, classified in class 514, subclass 44.

   V. Claims 41-44, drawn to a method of treatment using a composition comprising an antisense compound targeted to a nucleic acid encoding Fas and a chemotherapeutic agent, classified in class 514, subclass 44.

During a telephone conversation with Jane Massey Licata on December 10, 2001 a provisional election was made with traverse to prosecute the invention of Group V, claims 41-44. On December 10, 2001, Applicant submitted a preliminary amendment which canceled claims 1-44 and submitted new claims 45-58, all of which are drawn to the invention of Group V, and, therefore renders the restriction requirement moot.

2. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Double Patenting

3. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

4. Claims 45-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27 and 28 of U.S. Patent No. 6,133,031. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims overlap in scope with the patented claims. For example, instant claims

The instantly claimed general methods of treatment using antisense targeted to focal adhesion kinase of claims 45-54 would encompass the narrower methods of treating neovascularization in patented claim 28, and would be encompassed in the methods of inhibiting expression of focal adhesion kinase of patented claim 27.

5. Claims 45, 46 and 48-54 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 and 16 of copending Application No. 09/615,352. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of instant claims 45, 46 and 48-54 would embrace the methods of claims 6 and 16 of co-pending application 09/615,352. Claims 6 and 16 of 09/615,352 recite a method of treating a neovascular disease of the eye comprising administering an oligonucleotide specific for FAK, wherein the oligonucleotide comprises a nucleic acid sequence including SEQ ID NO:2, which is identical to the disclosed SEQ ID NO:12 of the instant case, and therefore the methods of claims 45, 46 and 48-54 would encompass the method of claims 6 and 16 of co-pending application 09/615,352.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Since the Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of **ABANDONMENT** of this application.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 45-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting neovascularization in the eye using an antisense molecule targeted to human focal adhesion kinase and inhibiting the growth of melanoma tumors using antisense targeted to human focal adhesion kinase of SEQ ID NO:18, does not reasonably provide enablement for generally treating any focal adhesion kinase associated disease or condition or generally any cancer using antisense targeted to human focal adhesion kinase. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 45-58 are drawn broadly to methods of treating generally any disease or condition associated with focal adhesion kinase, including generally any type of cancer, using an antisense molecule targeted to focal adhesion kinase or said antisense administered with a chemotherapeutic agent, including 5-fluorouracil.

The specification provides examples wherein cells *in vitro* (cell culture) are treated with antisense targeted to human focal adhesion kinase and the expression of focal adhesion kinase is inhibited, SEQ ID NO:18 is used to inhibit the migration of cells in an in vitro migration assay. The specification provides an example wherein SEQ ID NO:18 inhibits the expression of focal adhesion kinase in melanoma cells *in vitro* (cell culture) and this inhibition is enhanced by coadministration of 5-FU, in vitro. Further, the specification provides an *in vivo* (whole organism) rabbit model wherein antisense targeted to focal adhesion kinase is administered intravitreally and inhibits neovascularization in the eye. Finally, the specification provides an

example wherein SEQ ID NO:18 is administered to xenograft mouse and the growth and metastasis of human melanoma cells is inhibited. The specification does not demonstrate that any other antisense oligonucleotide targeted to focal adhesion kinase (other than SEQ ID NO:18) is capable of inhibiting the growth of melanoma tumors *in vivo* (whole organism).

At the time the instant invention was made and even to date, the application of antisense *in vivo* (whole organism) application of antisense without direct evidence is a highly unpredictable endeavor due to target accessibility and delivery issues (see for example Branch, Green et al., Jen et al.). Cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, and the potential for non-antisense side effects. The field of antisense, to date, does not provide guidelines by which antisense can be routinely targeted to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a treatment effect.

The specification has provided limited guidance for one skilled in the art to practice the invention claimed, however, that guidance would not be sufficient for the skilled artisan to have practiced the claimed treatment methods over the broad scope claimed. One of the major hurdles to the *in vivo* (whole organism) application of antisense is the delivery of an antisense molecule to a target cell at a concentration effective to provide a treatment effect. The examples in the specification which demonstrate treatment effects for neovascularization provide guidance by which a treatment effect is provided when antisense can be delivered locally, by direct injection into the eye, at a high concentration. The claimed treatment methods, however, are drawn to

delivery of antisense systemically, to generally any target cell, for generally any FAK associated disorder. Further, the specification provides one example of treating a melanoma tumor in a mouse, but the details of delivery are unspecified, as to whether direct, local administration was used, or if the antisense was delivered systemically.

The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to FAK to generally any cell or tissue *in vivo* (whole organism) wherein systemic delivery is required, particularly to deliver said antisense at a concentration effective to result in a treatment effect for generally any FAK associated disease or cancer. One skilled in the art would not be expected to be able to apply the limited guidance provided by the specification for local administration to generally any disorder, nor would one skilled in the art be expected to be able to treat generally any cancer using any FAK targeted antisense based on the example of melanoma tumors using SEQ ID NO:18. Given the unpredictability of antisense methods of treatment *in vivo* (whole organism), it is unclear that the in vitro examples using FAK antisense to inhibit the expression of FAK in adenocarcinoma cells would correlate with treatment effects for generally any disease or cancer, including melanoma, *in vivo* (whole organism). In order to have practiced the invention, over the full scope claimed, one skilled in the art would have needed to undergo undue trial an error experimentation, beyond the teachings of the instant specification. Such undue experimentation would include the determination of what diseases, and cancers, besides neovascularization using locally administered antisense and treatment of melanoma using SEQ ID NO:18, can be treated by the inhibition of

FAK, what specific cells to target with FAK antisense for the treatment of a particular disease or cancer (besides neovascularization using locally administered antisense and treatment of melanoma using SEQ ID NO:18), and how to specifically deliver antisense targeted to FAK *in vivo* (whole organism) to a target cell at a concentration effective to result in inhibition of FAK to a degree required for a treatment effect for a disease or cancer which can not be treated by local/direct administration of an antisense molecule. Further, it would require that determination of whether or not any other cancer (besides melanoma) can be treated *in vivo* (whole organism) using SEQ ID NO:18 and whether the *in vitro* (cell culture) inhibition of FAK using other FAK targeted antisense would correlate with a treatment effect *in vivo* (whole organism). Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule *in vivo* (whole organism) for the broad scope of treating any disease by any method of delivery, using generally any FAK targeted antisense molecule. Given the art recognized unpredictability of the application of antisense *in vivo* (whole organism) this determination would not be routine, nor would the limited guidance provided for FAK antisense delivered locally be sufficient for one skilled in the art to deliver antisense systemically, to generally any target cell. Although antisense is considered to be a potential therapeutic, there are art recognized limitations to its applicability *in vivo* (whole organism), particularly problems with delivery, *in vivo* (whole organism) stability, *in vivo* accessibility and toxicity. To overcome the limitations to the *in vivo* (whole organism) application of antisense, one skilled in the art would

require specific guidance to predictably apply antisense in the treatment of FAK related disease, or cancer. The specification does not provide this specific guidance for treatment of any disease, or cancer using systemically delivered antisense, or for the treatment of melanoma using any antisense (other than SEQ ID NO:18), nor does the antisense field to date have such general guidelines.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The Examiner can normally be reached from 8:30 am to 6:30 pm, Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ANDREW WANG
PRIMARY EXAMINER

Karen A. Lacourciere

December 17, 2001